Image

AF/1600

Corres. and Mail

BOX AF

Docket No.: PF-0489-1 CON

Response Under 37 C.F.R. 1.116 - Expedited Procedure

Examining Group 1646

Certificate of Mailing

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop: Appeal Brief-Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on February 27, 2004.

By: _____ Printed: Katherine Stofer

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Tang et al.

Title: POLYNUCLEOTIDES ENCODING HUMAN MSP-9 PROTEIN (AS AMENDED)

Serial No.: 09/823,356 Filing Date: March 30, 2001

Examiner: Murphy, J. Group Art Unit: 1646

Mail Stop: Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL FEE SHEET

Sir:

Transmitted herewith are the following for the above-identified application:

1. Return Receipt Postcard; and
2. Brief on Appeal, including Appendix (46 pp., in triplicate).

The fee has been calculated as shown below.

Claims	Claims After Amendment		Claims Previously Paid For		Present Extra	Other Than Small Entity Rate	Fee		Additional Fee(s)
Total	20		20			x$18.00		$	0
Indept.	3		3			x$86.00		$	0
First Presentation of Multiple Dependent Claims						+290.00		$	0
							Total Fee:	$	0

X Fee for filing a Brief in support of an Appeal under 37 CFR 1.17(c): $ 330.00

X Please charge Deposit Account No. **09-0108** in the amount of : $ 330.00

The Commissioner is hereby authorized to charge any additional fees required under 37 CFR 1.16 and 1.17, or credit overpayment to Deposit Account No. 09-0108. **A duplicate copy of this sheet is enclosed.**

Respectfully submitted,

INCYTE CORPORATION

Date: February 27, 2004

Shirley A. Recipon
Reg. No. 47,016
Direct Dial Telephone: (650) 621-8555

Customer No.: 27904
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 845-4166

Docket No.: PF-0489-1 CON

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1646

Certificate of Mailing

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Appeal Brief-Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450
on February 27, 2004.
By: _____ Printed: Katherine Stofer

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Tang et al.

Title:	POLYNUCLEOTIDES ENCODING HUMAN MSP-9 PROTEIN (AS AMENDED)		
Serial No.:	09/823,356	Filing Date:	March 30, 2001
Examiner:	Murphy, J.	Group Art Unit:	1646

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed December 23, 2003, and received by the USPTO on December 29, 2003, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the $ **330.00** fee for the filing of this Brief.

This is an appeal from the decision of the Examiner rejecting claims 3, 5-7, 9, 11-12, 79, 80 and 83 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to **Incyte Pharmaceuticals, Inc., (now Incyte Corporation, formerly known as Incyte Genomics, Inc.)** (Reel 010204, Frame 0759)

which is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 3, 5-7, 9, 11-12, 79, 80 and 83
Claims allowed:	(none)
Claims canceled:	Claims 4, 8, 10, 17-26, 29-78
Claims withdrawn:	Claims 1, 2, 13-16, 27, 28, 81 and 82
Claims on Appeal:	Claims 3, 5-7, 9, 11-12, 79, 80 and 83 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

There were no amendments submitted after Final Rejection.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed, *inter alia,* to a polynucleotide sequence, complementary sequences, RNA equivalents of the polynucleotide sequence and naturally occurring variants of the polynucleotide sequence. The invention at issue is a polynucleotide sequence corresponding to a gene that is expressed in gastrointestinal, male reproductive, muscle, neoplastic, and immune response-related tissues of humans (Specification, e.g., at page 30, lines 7-9).

Appellants first identified the nucleic acids of SEQ ID NO:26 encoding the polypeptide of SEQ ID NO:9 (MSP-9) in Incyte Clone 1794154 from the prostate cDNA library (PROSTUT05) using a computer search for amino acid sequence alignments. The sequence of SEQ ID NO:26 was derived from several Incyte Clones (specification; page 29 lines 17-24). The claimed polynucleotide encodes a

polypeptide (SEQ IN NO:9) demonstrated in the patent specification to be a member of the membrane spanning protein family (e.g., at page 10, lines 26-31; and page 22, line 30 to page 23, line 5). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide encoded by the claimed polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

(6) ISSUES

1. Whether claims 3, 5-7, 9, 11-12, 79, 80 and 83 directed to polynucleotide sequences meet the utility requirement of 35 U.S.C. §101.

2. Whether claims 3, 5-7, 9, 11-12, 79, 80 and 83 meet the enablement requirement of 35 U.S.C. § 112, first paragraph, i.e., would the specification enable one of ordinary skill in the art to make and use the claimed polynucleotides, e.g., for toxicology testing, drug development, and the diagnosis of disease.

3. Whether claims 3, 5-7, 9, 11-12, 79, 80 and 83 meet the enablement requirement of 35 U.S.C. § 112, first paragraph, with respect to the claimed "variants."

4. Whether claims 3, 5-7, 9, 11-12, 79, 80 and 83 meet the written description requirement of 35 U.S.C. § 112, first paragraph with respect to the claimed "variants.".

5. Whether claim 7 meets the enablement requirement of 35 U.S.C. § 112, first paragraph, with respect to "in vivo transfection."

6. Whether the subject matter of claims 3, 5-7, 9, 11-12, 79 and 80 particularly point out and distinctly claim the metes and bounds of the claimed invention with respect to "naturally occurring," so as to satisfy the definiteness requirement of 35 U.S.C. §112, second paragraph.

(7) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

As to Issue 3

All of the claims on appeal are grouped together.

As to Issue 4

All of the claims on appeal are grouped together.

As to Issue 5

This issue pertains only to claim 7.

As to Issue 6

Claims 3, 5-7, 9, 11-12, 79 and 80 are grouped together.

(8) APPELLANTS' ARGUMENTS

Appellants note that the Examiner acknowledged the cancellation of claim 4 on page 2 of the September 23, 2003 Office Action in the amendment accompanying the response received by the Patent Office on December 20, 2002 (Paper No. 13). However, the Examiner states that claims 3-7, . . . including claim 4, are rejected (Office Action, September 23, 2003; page 3). Appellants arguments will therefore hereinafter reflect the fact that claim 4 was canceled.

ISSUE 1:

The rejection of claims 3, 5-7, 9, 11-12, 79, 80 and 83 **is Improper, as the Inventions of Those Claims Have a Patentable Utility as Set Forth in the Instant Specification, and/or a Utility Well Known to One of Ordinary Skill in the Art.**

Claims 3, 5-7, 9, 11-12, 79, 80 and 83 stand rejected under 35 U.S.C. § 101 based on the allegation that the claimed invention is not supported by either a credible, specific and substantial

asserted utility or a well-established utility (Office Action, September 23, 2003; page 3). Additionally, claims 3, 5-7, 9, 11-12, 79, 80 and 83 stand rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility . . . , one skilled in the art clearly would not know how to use the claimed invention (Office Action, September 23, 2003; page 5). These rejections allege in particular that:

- The instant application does not disclose the biological role of this protein or its significance . . . Novel biological molecules lack well-established utility and must undergo extensive experimentation (Office Action, September 23, 2003; page 3).
- The instant claims are drawn to a nucleic acid encoding a polypeptide which has an as yet undetermined function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification as MSP-9, the instant invention is incomplete (Office Action, September 23, 2003; pages 4-5).
- An expression profile does not have specific and substantial use without knowing the biological significance of the polypeptide being evaluated (Office Action, September 23, 2003; page 6).

A. The rejection of claims 3, 5-7, 9, 11-12, 79, 80 and 83 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well known to one of ordinary skill in the art

The invention at issue is a polynucleotide sequence corresponding to a gene that is expressed in gastrointestinal, male reproductive, muscle, neoplastic, and immune response-related tissues of humans (Specification, e.g., at page 30, lines 7-9). The claimed polynucleotide encodes a polypeptide demonstrated in the patent specification to be a member of the membrane spanning protein family (e.g., at page 10, lines 26-31; page 22, line 30 to page 23, line 5). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide encoded by the claimed polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Appellants submit with this brief the Declaration of Bedilion (already of record; originally submitted on December 16, 2002) describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Patent Examiner with respect to the utility of the claimed polynucleotide are without merit.

Appellants note that Appellants arguments and the Bedilion Declaration were filed on December 16, 2002, and received by the USPTO on December 20, 2002. This is in contrast to the inaccurate statements of the Examiner in the Office Action of September 23, 2003, page 2, in which the Examiner states that the Bedilion Declaration was filed on April 28, 2003, "the Declaration under 37 CFR 1.132 filed in Paper No. 15, 4/28/2003 . . ."

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotide can be used in gene expression monitoring applications that were well known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as a highly specific probe in a cDNA microarray:

> Persons skilled in the art would [on March 13, 1998] appreciate that a cDNA microarray that contained the SEQ ID NO:9-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain any of these polynucleotides, in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for cancer, and immunological and reproductive disorders for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration, ¶ 15)

The Patent Examiner does not dispute that the claimed polynucleotide can be used as a probe in cDNA microarrays and used in gene expression monitoring applications. Instead, the Patent Examiner contends that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. But the law has never required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotide in the absence of any knowledge as to the precise function of the protein encoded by it. The uses of the claimed polynucleotide in gene

expression monitoring applications are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*,

626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Toxicology testing, drug discovery, and disease diagnosis are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Bedilion Declaration accompanying this brief. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of the claimed polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Bedilion Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide.

The instant application is a continuation of, and claims priority to, Tang et al. (U.S. Ser. No. 09/039,307, filed March 13, 1998; hereinafter "the Tang '307 application"). The instant application and the Tang '307 application were filed with essentially identical specifications, with the exception of corrected typographical errors, a substitute Sequence Listing, and reformatting. Thus page and line numbers may not match as between the instant application and the Tang '307 application.

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Tang '307 application on March 13, 1998 would have understood that application to disclose the claimed polynucleotides to be useful for a number of gene expression monitoring applications, *e.g.*, as highly specific probes for the expression of those specific polynucleotides in connection with the development of drugs and the monitoring of the activity of such drugs. (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotides in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications. (Bedilion Declaration, ¶¶ 12 and 15).[1]

In connection with his explanations, Dr. Bedilion states that "the specification of the Tang '307 application would have led a person skilled in the art [on] March 13, 1998, who was using gene

---

[1]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Tang '307 specification, that the claimed polynucleotides would be useful in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

expression monitoring in connection with developing new drugs for the treatment of cancer, and immunological and reproductive disorders, to conclude that a cDNA microarray that contained the SEQ ID NO:9-encoding polynucleotides would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:9-encoding polynucleotides." (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [on March 13, 1998] appreciate that a cDNA microarray that contained the SEQ ID NO:9-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain any of these polynucleotides, in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for cancer, and immunological and reproductive disorders for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-March 13, 1998 publications showing the state of the art on March 13, 1998. (Bedilion Declaration, ¶¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include almost three and a half pages of text and six subparts (a)-(f), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on March 13, 1998 (and for several years prior to March 13, 1998) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be considered and evaluated in connection with the development of the drug" and how the teachings of the Tang '307 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Tang '307 application at the time it was filed "would have wanted their cDNA microarray to have a probe to a SEQ ID NO:9-encoding polynucleotide because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to March 13, 1998." (Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than

sufficient reason to compel the conclusion that the Tang '307 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotides.

Nowhere does the Patent Examiner address the fact that, as described, for example, on pages 58-59 and 69 of the Tang '307 application (corresponding to pages 57-58 and 67-68 of the instant application), the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed SEQ ID NO:26 polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); M.P.E.P. § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., **they are useful in analyzing compounds**)" (emphasis added))

Though Appellants need not so prove to demonstrate utility, there can be no reasonable dispute that persons of ordinary skill in the art have numerous uses for information about relative gene expression including, for example, understanding the effects of a potential drug for treating cancer, and immunological and reproductive disorders. Because the patent application states explicitly that the claimed polynucleotide is known to be expressed both in normal cells as well as neoplastic and immune response-related cells (see the instant application at page 30, lines 7-9), there can be no reasonable dispute that a person of ordinary skill in the art could put the claimed invention to such use. In other words, the person of ordinary skill in the art can derive more information about a potential drug

candidate for cancer, and immunological and reproductive disorders, or potential toxins, with the claimed invention than without it (see Bedilion Declaration at, e.g., ¶ 15, subparts (e)-(f)).

The Bedilion Declaration shows that a number of pre-March 13, 1998 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Tang '307 application was filed (Bedilion Declaration ¶¶ 10-14; and Tabs A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Declaration at Tab D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published shortly after the filing of the Tang '307 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
>
> * * *
>
> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.

* * *

> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal. . . . However, the current use of gene profiling yields a **pattern** of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible in vivo similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. [emphasis added]

Rockett et al., Differential gene expression in drug metabolism and toxicology: Practicalities, problems and potential, Xenobiotica 29(7):655 (1999).

In another article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. **The amplicons can also be used directly by, for example, arraying onto glass for expression analysis**, for DNA binding assays, or for any direct DNA assay. [emphasis added]

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, Proceedings of the National Academy of Sciences USA 94:8945 (Aug. 1997).

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Dr. Bedilion in his

declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., *supra*:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis 24:153 (1999); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology – potentials and limitations, Toxicology Letters 112-113:467 (2000).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA arrays to toxicology, Environmental Health Perspectives 107(8):681 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator of the Nuwaysir paper, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was

responding. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patemt Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the rejections should be withdrawn regardless of their merit.

C. The uncontested fact that the claimed polynucleotides encode a protein in the membrane spanning protein family also demonstrates utility

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, it is undisputed that the claimed polynucleotides encode a protein having the sequence shown as SEQ ID NO:9 in the patent application and referred to as MSP-9 in that

application. Appellants have demonstrated that MSP-9 is a member of the membrane spanning protein family.

The Patent Office does not dispute any of the facts set forth in the previous paragraph. Neither does the Patent Office dispute that, if a polynucleotide encodes a protein that has a substantial, specific, and credible utility, then it follows that the polynucleotide also has a substantial, specific, and credible utility.

The Patent Office must accept the Applicants' demonstration that the polypeptide encoded by the claimed polynucleotides is a member of the membrane spanning protein family and that utility is proven by a reasonable probability unless it can be demonstrated through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

Nor has the Examiner provided any evidence that any member of the membrane spanning protein family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the polypeptide encoded by the claimed polynucleotides must, like the other members of the membrane spanning protein family, be useful.

D. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these

databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Appellants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences, throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's invention of the polypeptide encoded by the claimed polynucleotides, the databases become even more powerful tools. Thus, the claimed invention adds more than incremental benefit to the drug discovery and development process.

Customers can, moreover, purchase the claimed SEQ ID NO:26 polynucleotide directly from Incyte, saving the customer the time and expense of isolating and purifying or cloning the polynucleotide for research uses such as those described *supra*.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotides are not "credible, specific and substantial asserted" utilities (Office Action, September 26, 2002; page 4). The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The precise biological role or function of an expressed polynucleotide is not required to demonstrate utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's

efficacy and toxicity. The Examiner would require, in addition, that the Appellants provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Membership in a class of useful products can be proof of utility

Despite the uncontradicted evidence that the claimed polynucleotides encode a polypeptide in the membrane spanning protein family, the Examiner refused to impute the utility of the members of the membrane spanning protein family to MSP-9. In the Office Action of September 26, 2002 the Patent Examiner takes the position that, unless Appellants can identify which particular biological function within the class of membrane spanning proteins is possessed by MSP-9, utility cannot be imputed. To demonstrate utility by membership in the class of membrane spanning proteins, the Examiner would require that all membrane spanning proteins possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Examiner addresses MSP-9 as if the general class in which it is included is not the membrane spanning protein family, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the membrane spanning protein family does not. The membrane spanning protein family is sufficiently specific to rule out any reasonable possibility that MSP-9 would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the class of membrane spanning proteins has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the MSP-9 encoded by the claimed polynucleotides is useful. It follows that the SEQ ID NO:26 polynucleotide also is useful.

Even if the Patent Examiner's "common utility" criterion were correct – and it is not – the membrane spanning protein family would meet it. It is undisputed that known members of the membrane spanning protein family are proteins involved in the transmission of signals across cell membranes. A person of ordinary skill in the art need not know any more about how the claimed invention participates in the transmission of signals across cell membranes to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given membrane spanning protein carries out a particular role in the transmission of a particular signal across cell membranes. The Examiner then goes on to assume that the only use for MSP-9 absent knowledge as to how the membrane spanning protein actually works is further study of MSP-9 itself. This is not so.

As demonstrated by Appellants, knowledge that MSP-9 is a membrane spanning protein is more than sufficient to make it useful for the diagnosis and treatment of cancer, and immunological and reproductive disorders. Indeed, MSP-9 has been shown to be expressed in gastrointestinal, male reproductive, muscle, neoplastic, and immune response-related tissues of humans. The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

C. The uses of the claimed polynucleotides in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

The Patent Examiner's rejection of the claims at issue is tantamount to a rejection on the ground that the use of an invention as a tool for research is not a "substantial" use. Because the Patent Examiner's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be withdrawn.

There is no authority for the proposition that use as a tool for research is not a substantial utility.

Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (M.P.E.P. § 2107):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

The Patent Office's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the Patent Office's Training Materials to be useful, as are polynucleotide sequences used, for example, as markers.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete.

(Bedilion Declaration at ¶ 15.)

The use of the claimed invention as a research tool in toxicology testing is specific and substantial. While it is true that all polynucleotides expressed in humans have utility in toxicology testing based on the property of being expressed at some time in development or in the cell life cycle, this basis for utility does not preclude that utility from being specific and substantial. A toxicology test using any particular expressed polynucleotide is dependent on the **identity** of that polynucleotide, not on its biological function or its disease association. The results obtained from using any particular human-expressed polynucleotide in toxicology testing is specific to both the compound being tested and the polynucleotide used in the test. **No two human-expressed polynucleotides are interchangeable for toxicology testing** because the effects on the expression of any two such polynucleotides will differ depending on the identity of the compound tested and the **identities** of the two polynucleotides. It is not necessary to know the biological functions and disease associations of the polynucleotides in order to carry out such toxicology tests. Therefore, at the very least, the claimed polynucleotides are specific controls for toxicology tests in developing drugs targeted to other polynucleotides, and are clearly useful as such.

As an example, any histone gene expressed in humans can be used in a specific and substantial toxicology test in drug development. A histone gene may not be suitable as a target for drug development because disruption of such a gene may kill a patient. However, a human-expressed histone gene is surely an excellent subject for toxicology studies when developing drugs **targeted to other genes**. A drug candidate which alters expression of a histone gene is toxic because disruption of such a pervasively-expressed gene would have undesirable side effects in a patient. Therefore, when testing the toxicology of a drug candidate targeted to another gene, measuring the expression of a histone gene is a good measure of the toxicity of that candidate, particularly in *in vitro* cellular assays at an early stage of drug development. The utility of any particular human-expressed histone gene in toxicology testing is specific and substantial because a toxicology test using that histone gene cannot be replaced by a toxicology test using a different gene, including any other histone gene. This specific and substantial utility requires no knowledge of the biological function or disease association of the histone gene.

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include diagnostic assays (Specification, e.g., at pages 59-60), chromosomal mapping (e.g., at pages 61-62), etc.

D. The Patent Examiner failed to demonstrate that a person of ordinary skill in the art would reasonably doubt the utility of the claimed invention

Based principally on citations to scientific literature identifying some of the difficulties involved in predicting protein function, the Examiner rejected the pending claims on the ground that the Appellants cannot impute utility to the claimed invention based on the homology between the encoded polypeptide, MSP-9, and another polypeptide undisputed by the Examiner to be useful. The Patent Examiner's rejection is both incorrect as a matter of fact and as a matter of procedural law.

While the Examiner has cited literature identifying some of the difficulties that may be involved in predicting protein function, none suggests that functional homology cannot be inferred by a reasonable probability in this case. Doerks et al., Trends in Genetics 14:248-250 (1998); Brenner et al., Trends in Genetics 15:132-133 (1999); Bork et al., Trends in Genetics 12:425-427 (1996). Importantly, none contradicts Bork's later findings that there is a 70% accuracy rate for bioinformatics-based predictions in general, and a 90% accuracy rate for the prediction of functional features by homology. Bork, Genome Research 10:398-400 (2000). At most, articles cited by the Examiner individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

The literature cited by the Examiner may show that Appellants cannot prove function by homology with **certainty**, but Appellants need not meet such a rigorous standard of proof. Under the applicable law, once the Appellants demonstrate a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. See *In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not made such a showing and, as such, the Patent Examiner's rejection should be withdrawn.

The Examiner uses the teachings of Doerks et al. to assert that "sequence-to-function methods of assigning protein function are prone to errors" and that these errors "can be due to sequence similarity of the query region to a region of the alleged similar protein that is not the active site, as well as homologs that did not have the same catalytic activity because active site residues of the characterized family were not conserved" (Office Action, September 26, 2002; page 5). Doerks et al. examined 1300 protein sequences that were in "uncharacterized protein families" (Doerks et al., page 248, column 1, paragraph 2; page 250, column 1, paragraph 2). These sequences comprise a sample set chosen specifically because of difficulties in functional annotation. Thus, this reference is not relevant to the general validity of using sequence homology to assign protein function. In fact, Bork (one of the coauthors of the Doerks et al. reference) has shown that there is a 70% accuracy rate for bioinformatics-based predictions in general, and a 90% accuracy rate for the prediction of functional features by homology. Bork, Genome Research 10:398-400 (2000).

The Examiner cites Brenner et al. as further evidence that "accurate inference of function from homology must be a difficult problem" (Office Action, September 26, 2002; page 5). The difficulty of this problem is not relevant to the issue at hand. In spite of the "difficulty of this problem," Bork (2000) has shown that the prediction of functional features by homology has a 90% accuracy rate (Bork (2000), Table 1 on page 399). In fact, this 90% accuracy rate was determined in part from the data presented by Brenner et al. (see the citation of Brenner et al. (1999) in the fifth column of Table 1 of Bork (2000)). The legal standard for utility requires only that one of skill in the art would **more likely than not** believe the utility of the claimed invention. Therefore, the disclosure in Bork (2000) of a 90% accuracy rate for the prediction of functional features by homology shows that such methods are more than adequate for supporting a patentable utility.

In further support of the rejection, the Examiner cites the findings of Bork et al. (1996) that "the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts" (Office Action, September 26, 2002; page 5). However, this reference does not negate the fact that there is a 90% accuracy rate for the prediction of functional features by homology,

as disclosed by Bork (2000). At most this reference shows that errors can occur in functional assignment. Bork (2000) does not show that errors do not occur; however, this later Bork reference quantifies the error rate at about 10%.

The references cited by the Examiner show that there may be difficulties and errors involved in predicting protein function by homology. However, these references do not contradict the fact that such methods are accurate more often than not. As such, one of skill in the art would **more likely than not** believe that MSP-9 had the utilities of the family of membrane spanning proteins.

As the cited evidence is completely insufficient to support the rejections of the claims, the outstanding rejections must be withdrawn for this reason alone. The only relevant evidence of record shows that a person of ordinary skill in the art would not doubt that the polypeptide encoded by the claimed polynucleotides is in fact a member of the family of membrane spanning proteins. Membrane spanning proteins are known to have specific utility.

IV. By Requiring the Patent Appellant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. See *supra* § II.B. Thus, the Training Materials cannot be applied consistently with the law.

ISSUE 2: To the Extent the Rejection of the Patented Invention under 35 U.S.C. § 112, First Paragraph, Is Based on the Improper Rejection for Lack of Utility under 35 U.S.C. § 101, it Must Be Reversed.

The rejection set forth by the Patent Examiner is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

ISSUE 3: The Rejection under 35 U.S.C. §112, first paragraph, for Alleged Lack of Enablement is Improper, as the Specification is Enabling for the Claimed Variants

Claims 3, 5-7, 9, 11-12, 79-80 and 83 were rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter of the invention in such a way as to enable one of skill in the art to make and/or use the claimed variants (Office Action, September 23, 2003; page 9). In particular, Examiner asserts that the Specification does not describe how to make and/or use polynucleotides encoding naturally occurring polypeptides at least 90% identical to SEQ ID NO:26 as well as polypeptides 90% identical to SEQ ID NO:9. Such, however,

is not the case.

A. The Claimed Invention Can be Made and Used Without Undue Experimentation

As a preliminary matter, note that claim 3, for example, recites not only that the polynucleotides encode polypeptides which are at least 90% identical to SEQ ID NO:9, but also that they have "a naturally occurring amino acid sequence." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:9 (the amino acid sequence of MSP-9) and SEQ ID NO:26 (the polynucleotide sequence encoding MSP-9), one of skill in the art would be able to routinely make or obtain from natural sources "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence [of SEQ ID NO:9]."

1. The Specification Teaches Resources from which Variants of SEQ ID NO:26 and SEQ ID NO:9 May be Obtained, as well as Well Known Techniques for Their Isolation

The specification teaches that nucleic acids encoding the MSP-9 (SEQ ID NO:9) of the present invention were first identified in Incyte Clone 1794154 from the prostate cDNA library (PROSTUT05). The specification continues by listing numerous cDNA libraries and the clones isolated from these cDNA libraries (both tumor and non-tumor) and the clones which contained the nucleic acids combined to arrive at SEQ ID NO:26 (Specification, page 29, lines 17-24). These clones are available from Appellants' assignee, Incyte Corporation.

One of skill in the art would be able to isolate and identify variants of SEQ ID NO:26 which codes for variants of SEQ ID NO:9 by screening the clones taught on page 29 for variations in the polynucleotide sequences of each clone. For example, using primers designed from SEQ ID NO:26, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. See, e.g., page 21, line 16 to page 22, line 2; page 36, lines 7-16; page 57, line 20 to page 58, line 10; and Example VI at pages 67-68. Thus, one skilled in the art need not make and test vast numbers of polynucleotides that encode

polypeptides based on the amino acid sequence of SEQ ID NO:9. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides, and their encoded polypeptides, that already exist in nature. By adjusting the nature of the probes or nucleic acids (i.e., non-conserved, conserved, or highly conserved) and the conditions of hybridization (maximum, high, intermediate, or low stringency), one can obtain variant polynucleotides of SEQ ID NO:26 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:9 recited by the present claims using conventional techniques of recombinant protein production. Such experimentation is considered routine when looking for mutations and genetic variablity.

a. The Specification Teaches the Making of Variants of SEQ ID NO:26

The Examiner asserts that "Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polynucleotides and encoded polypeptides which the specification only teaches one skilled in the art to test for functional variants" (Office Action of September 23, 2003, page 11). Appellants strongly disagree.

The specification teaches how to make the claimed polynucleotide variants using methods which extend partial nucleotides to full length (specification, e.g., page 36 line 17 to page 38 line 5; Example V, page 65 line 26 to page 67 line 31). One of skill in the art would know how to design and use primers to extend antisense and sense polynucleotides to facilitate the extension of the known sequence "outward" generating amplicons containing new unknown nucleotide sequence for the region of interest. Methods of primer design using software programs such as OLIGO 4.06 are taught in the specification (specification, page 66, lines 1-4). Thus, the specification enables the making of polynucleotide variants of SEQ ID NO:26.

b. The Specification Teaches the Making of Variants of SEQ ID NO:9

The specification teaches how to make the claimed polypeptide variants using methods which utilize either a variety of molecular biology techniques to express MSP proteins or a variety of chemical procedures to synthesize MSP peptides (page 38 line 22 to page 46 line 19). Using the variant polynucleotides identified by methods taught in the specification, *supra,* one of skill in the art would be able to make the encoded variant polypeptides using direct synthesis and/or in combination with sequences from other proteins, e.g., fusion proteins (specification, page 39 lines 26-28). Such

molecular biology techniques are considered routine by one of ordinary skill in the art when identifying sequence variations. Thus, the specification enables the making of polypeptide variants of SEQ ID NO:9.

B. Sequence Variation Does Not Necessarily Alter Biological Function and Therefore the Examiner Has Not Made a *Prima facie* Case for Lack of Enablement

The Examiner asserts that "even single amino acid changes or differences in the amino acid sequence of a protein **can** have dramatic effects on the protein's function" and that "a single amino acid change in a protein's sequence **can** drastically affect the structure of the protein and the architecture of an entire cell" (Office Action, September 26, 2000; page 7; emphasis added), and cites Voet et al. (in Biochemistry, John Wiley & Sons, 1990, pages 126-128 and 228-234) as support. These assertions demonstrate that the Examiner has based the alleged lack of enablement on the mere **possibility** that mutations can sometimes alter the biological function of a naturally occurring polypeptide. This conclusion ignores Bork (Genome Res. (2000) 10:398-400, of record), which teaches that the prediction of functional features by homology has a 90% accuracy rate, and that the accuracy rate for all bioinformatics predictions has a 70% accuracy rate (Table 1 of Bork (2000)). While there may be a number of examples in which the assignment of function by sequence homology is not perfectly accurate, this does not contradict the findings of Bork (2000) that, **in general**, sequence homology is an accurate method for assigning biological function.

For example, the Examiner states that Voet et al. teach that "a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages" (Office Action, September 26, 2002; pages 7-8). However, the hemoglobin having the single amino acid change cited in the Office Action **retains the ability to carry oxygen**. In this case, the function of the hemoglobin polypeptide has been altered by a single amino acid mutation, but that function has not been entirely eliminated. Therefore, one of skill in the art would still be able to use the altered hemoglobin polypeptide **in the exact same manner as one would use the nonaltered**

polypeptide, even though the results would not be exactly the same as if the nonaltered polypeptide was used. Likewise, one of skill in the art would know how to use the recited variants of SEQ ID NO:9; even if the results achieved from using the recited variants were not equivalent to the results achieved from using the SEQ ID NO:9 polypeptide, one of skill in the art would still be able to achieve **some** level of results by using the recited variants in the same manner as the SEQ ID NO:9 polypeptide. This is all that is required to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

The Examiner has failed to demonstrate that one of skill in the art could not make and use the claimed polynucleotides encoding polypeptide variants comprising naturally occurring amino acid sequences at least 90% identical to SEQ ID NO:9. The Examiner has only provided an isolated example in which mutations can sometimes result in a change of the biological activity of a naturally occurring polypeptide. The cited reference has no bearing on the ability of a skilled artisan to screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides, and their encoded polypeptides, that already exist in nature, without undue experimentation.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any **reasons** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited polynucleotides encoding polypeptide variants of SEQ ID NO:9, or the recited polynucleotide variants of SEQ ID NO:26. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited variants of SEQ ID NO:9 and SEQ ID NO:26.

For at least the above reasons, withdrawal of this rejection is requested.

ISSUE 4: The Rejection under 35 U.S.C. §112, first paragraph, for Alleged Lack of Written Description is Improper, as the Specification Provides an Adequate Description of the Claimed Variants

Claims 3, 5-7, 9, 11-12, and 79-80 were rejected under 35 U.S.C. § 112, first paragraph, as being based on a specification which allegedly fails to reasonably convey to one of skill in the art that the Appellants had possession of the claimed invention at the time the application was filed. The Examiner asserts that "the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a nucleic acid with a sequence as set forth in SEQ ID NO:[26], and the polypeptide of SEQ ID NO:[9] is insufficient to describe the genus" (Office Action, September 23, 2003; page 13).

In particular, the Examiner asserts that the specification fails to provide sufficient descriptive information, . . . defining characteristics of the polypeptides, . . . such as the untranslated regions, introns, and promoter sequences . . ." (Office Action of September 23, 2003, page 14). On the contrary, it is Appellants' position that the specification does provide sufficient descriptive information, i.e., definitive structural features of the genus of polynucleotides and encoded polypeptides such that one of skill would be able to identify the claimed variants.

A. Legal Requirements

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed.
> Vas-Cath, Inc. v. Mahurkar, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which

provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. [footnotes omitted]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

B. The specification provides an adequate written description of the claimed "variants" of SEQ ID NO:9 and SEQ ID NO:26.

The subject matter encompassed by claims 3, 5-7, 9, 11-12, and 79-80 is either disclosed by the specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 3 recites a polynucleotide encoding a polypeptide "comprising a naturally occurring amino acid sequence at least 90% identical to" the amino acid sequence of SEQ ID NO:9. Similarly, the "variant" language of independent claim 11 recites "a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to" the sequence of SEQ ID NO:26. The amino acid sequence of SEQ ID NO:9 and the polynucleotide sequence of SEQ ID NO:26 are explicitly disclosed in the specification. See, for example, the Sequence Listing. Variants of SEQ ID NO:9 and SEQ ID NO:26 are described in the Specification at, for example, page 11, lines 5-9 and 22-25; page 14, line 10 to page 15, line 3; page 15, lines 9-12; page 22, lines 27; page 35, lines 10-13; page 35, line 19 to page 36, line 21; and page 38, line 22 to page 39, line 18. One of ordinary skill in the art would recognize polynucleotide sequences which are variants having a polynucleotide sequence at least 90% identical to SEQ ID NO:26, or which encode polypeptide variants having an amino acid sequence at least 90% identical to SEQ ID NO:9.

Given any naturally occurring polynucleotide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:26, and whether it encoded a variant of SEQ

ID NO:9. Accordingly, the specification provides an adequate written description of the recited polynucleotide variants of SEQ ID NO:26 and polynucleotides encoding polypeptide variants of SEQ ID NO:9.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than functional characteristics. For example, the language of independent claims 3 and 11 recites chemical structure to define the claimed genus:

> 3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:
> a) a polypeptide comprising [the amino acid sequence of SEQ ID NO:9], and
> b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to [the amino acid sequence of SEQ ID NO:9].
>
> 11. An isolated polynucleotide selected from the group consisting of:
> a) a polynucleotide comprising [the polynucleotide sequence of SEQ ID NO:26],
> b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to [the polynucleotide sequence of SEQ ID NO:26],
> c) a polynucleotide completely complementary to the polynucleotide of a),
> d) a polynucleotide completely complementary to the polynucleotide of b), and
> e) an RNA equivalent of a)-d).

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:9 and SEQ ID NO:26.

The Specification defines specific structural domains related to MP proteins generally at page 2, lines 4-25; page 4, line 22 to page 5, line 7; page 29, line 26 to page 30, line 5. Structural domains within the claimed MSP-9 polypeptides are three potential N-glycosylation sites at residues N667, N668, N835; six potential cAMP- and cGMP-dependent protein kinase phosphorylation sites at residues S79, T204, S409, S434, S658, and S767; seventeen potential casein kinase II phosphorylation sites at residues S64, T65, S113, S284, T398, S409, S418, T437, T449, S518, S576, T591, S611, T708, T717, S735, and S838; twenty five potential protein kinase C phosphorylation sites at residues T2, T28, S45, T55, S113, S124, S308, T347, T365, T384, S393, T404, S418, T429, T430, S454, S537, S565, S572, S583, T600, S607, T654, T670, and T732; one potential tyrosine kinase phosphorylation site at residue Y918; and a potential signal peptide sequence from about M1 to P23. MSP-9 shares 28% identity with human type I, p80 IL-1-receptor intracellular domain ligand (WO9640907-A1) (Specification; page 29, line 26 to page 30, line 5).

In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides and polypeptides. The polynucleotides defined by the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base the written description inquiry "on whatever is now claimed," the Patent Office failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that, rather than being a large variable genus, the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078, of record). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with

<90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

The present application is directed, *inter alia*, to polynucleotides encoding membrane spanning proteins, including polynucleotides encoding membrane spanning proteins related to the amino acid sequence of SEQ ID NO:9. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as membrane spanning proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:9. The "variant language" of the present claims recites a polynucleotide encoding a polypeptide comprising "a naturally occurring amino acid sequence at least 90% identical to [the amino acid sequence of SEQ ID NO:9]" (note that SEQ ID NO:9 has 950 amino acid residues). This variation is far less than that of polynucleotides encoding all potential membrane spanning proteins related to SEQ ID NO:9, i.e., those membrane spanning proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:9.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those cases was based on the state of the art at essentially the "dark ages" of recombinant DNA technology.

The present application has a priority date of March 13, 1998. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been

compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:9 and SEQ ID NO:26, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

4. Summary

The Patent Examiner failed to base the written description inquiry "on whatever is now claimed." Consequently, the Examiner did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:9 and SEQ ID NO:26. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Examiner.

For at least the reasons set forth above, the specification provides an adequate written description of the claimed subject matter, and this rejection should be reversed.

ISSUE 5: The Rejection of Claim 7 is Improper, as the Specification Discloses at least One Method for Making and Using Cells Transformed With the Polynucleotide of SEQ ID NO:26

Claim 7 was rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter of the invention in such a way as to enable one of skill in the art to make and/or use the claimed cells (Office Action, September 26, 2002, page 10; Final Office Action, September 23, 2003, page 15). In particular, the Examiner asserts that the Specification

"does not reasonably provide enablement for in vivo transfection" and that "there are no actual or prophetic examples that disclose how to make or use host cells that comprise a DNA sequence as set forth in SEQ ID NO:26 in an animal" (*Id*). Such, however, is not the case.

Claim 7 recites a "cell transformed with a recombinant polynucleotide" comprising a promoter sequence operably linked to a polynucleotide encoding a polypeptide of SEQ ID NO:9. Support for transformed cells can be found in the specification at, for example, page 22, lines 9-18; page 40, line 4 to page 44, line 30; page 45, line 29 to page 46, line 19; page 51, line 1-13; page 52, line 26 to page 53, line 1; and page 70, lines 12-22. One of skill in the art would know how to make and use the claimed transformed cells, based on the specification and the state of the art at the time the application was filed, without undue experimentation.

The Examiner insists that, in order for the claim to be enabled, the specification must separately enable "host cells in an animal." Appellants respectfully disagree. There is no such requirement that "host cells in an animal" be separately enabled because the claimed "transformed cells" are already fully enabled by the specification. However, even if it was proper for the Patent Office to require enablement of "host cells in an animal," the specification would meet this requirement. According to the M.P.E.P.:

> As long as the specification discloses **at least one** method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir.), *cert. denied*, 484 U.S. 954 (1987). (M.P.E.P. § 2164.01(b); emphasis added)

Therefore, if one method of making and using "host cells in an animal" is enabled by the specification, then the requirements of 35 U.S.C. § 112, first paragraph are met for "host cells in an animal."

The Examiner focuses on the alleged lack of enablement of *in vivo* transfection. However, there is no requirement that this particular method be enabled in order for the claimed **transformed cells** to be enabled. As the Examiner recognizes, the application is "enabling for a host cell in culture comprising a polynucleotide with the sequence as set forth [in SEQ ID NO:26]" (Office Actions:

September 26, 2002, page 10; September 23, 2003, page 16), and cells isolated from a transgenic animal which comprise the polynucleotide of SEQ ID NO:26 (Office Action of September 23, 2003, page 16). Thus, one of skill in the art would be able to make the claimed transformed cells in culture **and in vivo** e.g., within a transgenic animal, and use them, for example, to produce the encoded polypeptides. Therefore, the claim at issue is fully enabled.

Transgenic methods of producing animals comprising transformed cells are also well known in the art. For example, Hadjantonakis et al. state that "[o]ver the past decade the production of targeted and transgenic lines of mice has become commonplace, with current technology allowing the creation of mutations at base pair resolution" (Hadjantonakis et al. (2001) Histochem. Cell Biol. 115:49-58; abstract, of record). In addition, Hadjantonakis et al. disclose that the production of a transgenic animal through the introduction of DNA into zygotes by pronuclear injection "is straightforward and has been achieved in a wide variety of animals" (at page 49, right column, last paragraph to page 50, left column, first paragraph). Therefore, one of skill in the art would routinely be able to make a host cell in an animal by applying well known transgenic methods, without undue experimentation.

There is no requirement for *in vivo* transfection to be enabled, as the Examiner asserts, because transgenic methods of making "host cells in an animal" are enabled. The Examiner cites Eck & Wilson (in Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth edition, McGraw Hill, New York, 1996, pages 77-101) as support that *in vivo* gene expression is complicated by numerous factors "which have not been shown to be overcome by routine experimentation" (Office Action, September 26, 2002; pages 10-11). However, the section of the Eck & Wilson reference cited in the Office Action (page 81, column 2, second paragraph to page 82, column 1, second paragraph) speaks only to *in vivo* gene expression in the context of transfecting an animal with a viral vector during gene therapy, and has no bearing on transgenic methods as described by Hadjantonakis et al. The Eck & Wilson reference is irrelevant because it does not address alternative ways of making and using host cells in an animal, such as by transgenic methods. Thus, there is no evidence that "host cells in an animal," or the claimed "transformed cells," are not enabled.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

The first paragraph of § 112 requires nothing more than objective enablement. How

> such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any **reasons** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited cells transformed with a polynucleotide comprising SEQ ID NO:26. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited cells transformed with a polynucleotide comprising SEQ ID NO:26.

For at least the above reasons, reversal of this rejection is requested.

ISSUE 6: The Rejection under 35 U.S.C. §112, second paragraph, for Indefiniteness is Improper, as the Specification Clearly and Distinctly Claims the Subject Matter of the "Invention" and Determines the Metes and Bounds of Claims 3, 11 and 12 and Claims Which Depend Therefrom

Claims 3, 5-7, 9, 11-12, 79 and 80 were rejected as indefinite for allegedly "failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner asserts:

> Claims 3, 11 and 12 are indefinite in the recitation of the term "naturally occurring." It is unclear **whether this term imposes a required limitation on the claim**, such that it only encompasses, for example, polynucleotides amplified from human cDNA, or only sequences produced by digestion with restriction enzymes of DNA isolated from tissue that contains polynucleotides encoding the polypeptide, or it the claim encompasses all polynucleotide sequences that encode the polypeptide. Therefore, the metes and bounds of the claim are unclear (emphasis added) (Office Action of September 23, 2003, page 17).

The Examiner stated that "[c]laims 4-9,79-80 are rejected due to their dependence on claims 3, 11 and 12." (Office Action of September 23, 2003, page 17).

At the outset Appellants note that claim 8 was canceled at the time of filing the continuation application (March 30, 2001), and claim 4 was canceled in the response filed December 16, 2002, received by the Patent Office on December 20, 2002. Furthermore, the dependent claims pertaining to ISSUE 6 do not depend from claim 12. Therefore, claim 5-7, 9, 79 and 80 stand rejected under 35 U.S.C. §112, second paragraph, due to their dependence on claims 3 or 11.

The standard for "definiteness" is that the claims define patentable subject matter with a reasonable degree of precision and particularity. See *In re Miller*, 169 USPQ 597, 599 (CCPA 1971); *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). See also MPEP §706.03(d). In this regard, the Supreme Court has indicated that the primary purpose of claim language is to give "fair" notice of what would constitute the infringement of a claim. See *United Carbon Co. v. Binny & Smith Co.*, 317 U.S. 228, 55 USPQ 381 (1942). In other words, the basic purpose of 35 U.S.C. §112, second paragraph is to require a claim to reasonably apprize those skilled in the art of the scope of the invention defined by that claim and give fair notice of what constitutes infringement of the claim. See *Antonious v. Pro Group Inc.*, 217 USPQ 875, 877 (6th Cir. 1983). The present claims meet the legal standards required by 35 U.S.C. § 112, second paragraph.

At page 14 of the specification, Appellants define "naturally occurring" as "substantially purified MSP obtained from any species, particularly mammalian, including bovine, ovine, porcine, murine, equine, and preferably the human species, from any source whether natural, synthetic, semi-synthetic, or recombinant" (specification, page 14 lines 2-5). Thus, the term "naturally occurring" would be understood by one of skill in the art and even by an unskilled person of the art to be that which occurs in nature. Further, "variants" are defined at page 22, lines 19-27, as referring to "an amino acid sequence that is altered by one or more amino acids."

The term "naturally occurring" is not a limitation of the claimed polynucleotides themselves, **as the Examiner seems to imply** (Papers No. 10 and No. 16). The term "naturally occurring" **is a limitation** of the polynucleotide ***sequences*** comprised by the claimed polynucleotides; similarily, it **is a limitation** of the amino acid ***sequences*** comprised by the recited polypeptides encoded by the claimed polynucleotides. For example, the "variant" language of claim 3 recites an isolated polynucleotide encoding "a polypeptide comprising a **naturally occurring amino acid sequence** at least 90%

identical to [the amino acid sequence of SEQ ID NO:9]." Similarly, the "variant" language of claims 11 and 12 recite an isolated polynucleotide "comprising a **naturally occurring polynucleotide sequence** at least 90% identical to [the polynucleotide sequence of SEQ ID NO:26]." The term "naturally occurring," in the context of polynucleotide and amino acid sequences, is supported in the specification at, for example, page 14, lines 2-5 and 10-17; page 20, lines 7-11; and page 39, lines 12-14. One of skill in the art would reasonably understand that the recitation of "naturally occurring" sequences encompasses **any sequence which occurs in nature**.

Furthermore, one of skill in the art would reasonably understand, based on the language of the claims, that the claimed isolated polynucleotides in the preamble of claims 3, 11 and 12 are not limited to these molecules which are themselves naturally occurring; they further include actual physical molecules which can be made by man. For example, the claimed isolated polynucleotides could be isolated from a natural source, they could be amplified by PCR from a natural source, they could be produced by recombinant DNA techniques, or they could be chemically synthesized *de novo*. The chemical structures of these man-made polynucleotides are based on the ***information provided by*** the naturally occurring amino acid sequence of SEQ ID NO:9, and the naturally occurring polynucleotide sequence of SEQ ID NO:26. Therefore, the claims are definite in their recitation of isolated, man-made polynucleotides which have sequences derived from naturally occurring molecules.

Hence Appellants have defined "naturally occurring such that one of ordinary skill in the art can determine the metes and bounds of the claimed invention and respectfully request reversal of this rejection under 35 U.S.C. § 112, second paragraph.

(9) CONCLUSION

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Action and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor are they supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide

and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, "like a nose of wax," to target rejections of claims to polypeptide and polynucleotide sequences where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specification as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

Due to the urgency of this matter, including its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This brief is enclosed in triplicate

Respectfully submitted,

INCYTE CORPORATION

Date: 26, February 2004

Shirley A. Recipon

Shirley A. Recipon
Reg. No. 47,016
Direct Dial Telephone: (650) 621-8555

Date: 26 February 2004

Cathleen M. Rocco

Cathleen M. Rocco
Reg. No. 46,172
Direct Dial Telephone: (650) 845-4587

Customer No.: 27904
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

APPENDIX - CLAIMS ON APPEAL

3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:

a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17, and

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-17.

5. An isolated polynucleotide of claim 4, comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34.

6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.

7. A cell transformed with a recombinant polynucleotide of claim 6.

9. A method of producing a polypeptide encoded by a polynucleotide of claim 3, the method comprising:

a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide of claim 3, and

b) recovering the polypeptide so expressed.

11. An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34,

c) a polynucleotide completely complementary to the polynucleotide of a),

d) a polynucleotide completely complementary to the polynucleotide of b), and

e) an RNA equivalent of a)-d).

12. An isolated polynucleotide comprising at least 1000 contiguous nucleotides of a polynucleotide selected from the group consisting of:

a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

79. A polynucleotide of claim 3, encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:9.

80. A polynucleotide of claim 11, comprising the polynucleotide sequence of SEQ ID NO:26.

83. An isolated polynucleotide of claim 11 selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:26,

b) a polynucleotide completely complementary to a polynucleotide of a), and

c) an RNA equivalent of a)-b).